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Evaluation of ciprofloxacin 500 mg twice daily for one week in treating uncomplicated gonococcal, chlamydial, and non-specific urethritis in men

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SUMMARY Ciprofloxacin, a quinolone antibacterial, was evaluated in the treatment of gonococcal, chlamydial, gonococcal and chlamydial, and non-gonococcal non-chlamydial urethritis. The dosage regimen used was 500 mg orally twice a day for seven days. Of the 56 patients evaulated, 22 had gonococcal infection only, 13 were infected with *Chlamydia trachomatis* only, seven had combined infection, and 14 were harbouring neither of these organisms. *Neisseria gonorrhoeae* was cleared in all the 29 patients with or without chlamydial infection. Of those who denied having sexual intercourse during the follow up period, post gonococcal urethritis (PGU) developed in 12 (63%) out of 19, *C trachomatis* was isolated again from 11 (78%) out of 14, and urethritis recurred in five (55%) out of nine patients with non-gonococcal non-chlamydial infection. There was also evidence that the dosage regimen used was only partially effective against *Ureaplasma urealyticum*.

Introduction

Urethritis is the commonest manifestation of sexually transmitted disease (STD) in England. In 1983 97 673 new cases of non-gonococcal urethritis (NGU) and 30 464 cases of gonorrhoea were diagnosed in men in clinics in England.[1] Reports from some countries showed that in about 60% of men with NGU *Chlamydia trachomatis* was the sole causative organism,[2] but in 23% to 40% of men with gonorrhoea and about 50% of women with gonorrhoea, *C trachomatis* was also present as a concurrent infection.[3-6] The widely practised treatment of gonorrhoea with penicillin or alternative agents (such as spectinomycin), which have no effect on *C trachomatis*, is therefore increasingly thought to be undesirable as patients presenting with both infections concurrently will probably have persistent chlamydial infection after the gonorrhoea has been cured.

Such persistent chlamydial infection may be completely silent or may give signs or symptoms of postgonococcal urethritis in men, with a possibility of later epididymitis, or of postgonococcal cervicitis in women, with a risk of spread to sexual partners or neonates and of pelvic inflammatory disease or perihepatitis. For example, up to 50% of men with gonorrhoea develop PGU, which is asymptomatic in about half the patients.[6] In 80% of patients with asymptomatic PGU the cause was unresolved chlamydial infection, which had been present concurrently with gonorrhoea before treatment.[7] Similarly, over 60% of women with combined gonococcal and chlamydial infection had persistent cervicitis after treatment with penicillin because the drug had failed to cure the chlamydial infection.[6 8]

None of the more recent ß lactam antibiotics is more effective than penicillin against chlamydiae.[9] Up to now tetracycline has been the only drug that was cheap and effective against gonococcal as well as chlamydial infection; but unacceptably high failure rates in gonorrhoea, especially in women, have been reported recently in the United States of America.[10] Moreover, in many areas of the world both chromosomal and plasmid encoded resistance of *Neisseria gonorrhoeae* have appreciably reduced the therapeutic options.[11]

Ciprofloxacin is a new quinolone antibacterial that differs from the best known quinolone, nalidixic acid, in having high intrinsic activity (a low minimum inhibitory concentration (MIC)) against both Gram negative and Gram positive bacteria.[12] Resistance to ciprofloxacin does not readily develop after serial subculture of bacteria in media containing this

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antimicrobial.

A single dose of ciprofloxacin 500 mg gives peak serum concentrations of 3 mg/l to 4 mg/l. Pharmacokinetic data indicate that ciprofloxacin has a large volume of distribution, which indicates that it has good tissue penetration. It has high in vitro activity against *N gonorrhoeae* (including strains resistant to penicillin and tetracycline), the MIC being 0·01 mg/l.[13] It is also active against *C trachomatis* (MIC 2 mg/l[13 14]), *Ureaplasma urealyticum* (MIC 0·5 mg/l to 2 mg/l[15]), and *Mycoplasma hominis* (MIC 0·25 mg/l to 0·5 mg/l[15]) in concentrations that are higher than those effective for gonorrhoea but still lie well within attainable peak blood concentrations.

Cumulative data on 1102 patients who were given ciprofloxacin show that only 7% developed minor side effects (unpublished communication, Bayer UK Limited).

We evaluated the efficacy of ciprofloxacin in men with gonococcal, chlamydial, gonococcal and chlamydial, or non-gonococcal and non-chlamydial urethritis. We also decided to observe the effect of ciprofloxacin on mycoplasmas in the last 14 patients.

Patients and methods

Heterosexual men were included in the study if they were over 18 years old, had not had an STD in the preceding three months, had not received an antibacterial agent in the preceding month, had a demonstrable urethral discharge, did not have any other STD, were not likely to default, had no history of allergy to quinolones, and gave informed signed consent. The study was approved by the local ethical committee

HISTORY, EXAMINATION, AND LABORATORY INVESTIGATIONS

Demographic data, past history, history of recent exposure, and symptoms and signs were recorded on precoded proformas.

Urethal specimens were collected with plastic loops for smears for Gram staining and were also inoculated directly on to modified Thayer-Martin medium for culturing for *N gonorrhoeae*. Gonorrhoea was diagnosed if Gram stained urethral smears showed Gram negative intracellular diplococci, with subsequent confirmation by culture. The diagnostic criterion of NGU was more than 5 polymorphonuclear leucocytes (PMNL) in at least five high power fields (hpf) (1000× magnifications). Specimens for *C trachomatis* and mycoplasmas were obtained with swabs made of sterile plain cotton wool on a thin metal wire (Medical Wire and Equipment Co, Corsham, Wiltshire) inserted 3 cm to 5 cm into the urethra and rotated several times. Swabs for *C trachomatis* were placed in transport medium and inoculated with centrifugation on to cycloheximide treated McCoy cells in plastic well plates. Growth was estimated after incubation for 72 hours by staining the cultures with periodic acid Schiff (PAS) reagent and screening for brilliant red cytoplasmic inclusions.[16] Swabs for mycoplasmas were placed in A3 × B transport medium and titrated in urea broth for *Ureaplasma* spp and arginine broth for *Mycoplasma* spp.

MICs for *N gonorrhoeae* and *C trachomatis* were measured as described previously.[12] MICs for mycoplasmas were measured as described by Taylor-Robinson and Furr in microtitre plates using a standardised inoculum of 10^3-10^4 colour changing units (ccu)/ml.[17]

Blood was taken initially and seven days later for full blood counts, liver function tests, and to measure urea and creatinine concentrations. A specimen of blood was also taken for syphilis serology tests, which were repeated after three months.

TREATMENT

Each patient was given seven days' supply of ciprofloxacin 500 mg, to be taken orally twice a day.

Patients were advised to abstain from sexual intercourse until they and their partners were cleared of infection, to avoid alcohol for one week so as to assess accurately the nature of any side effects, and to ask their sexual contacts to attend our women's clinics. Contact slips were issued and several patients interviewed by our social workers or contact tracers. Appointments for their sexual contacts were often arranged at the same time.

FOLLOW UP

Each patient was requested to return with a full bladder (having held urine for at least four hours) 1, 2, 3, 6, and 12 weeks after the start of treatment (or at any time in the event of any new development) and to bring back the ciprofloxacin tablets' container on the first follow up visit so that compliance could be checked.

At each visit the patients were interviewed regarding further sexual exposure (if this had been with the same partner they were asked whether or not the partner had been treated before sexual intercourse was resumed; if the partner had also attended our clinics the case sheets were cross checked), interim medication, and symptoms. This was followed by clinical examination, and urethral smears were taken for Gram staining. Specimens were collected for culturing for *C trachomatis* as well as *N gonorrhoeae* on the first two follow up visits, but for only *C trachomatis* at subsequent visits. If either of these organisms was isolated again or if a patient had overt urethritis at any time after treatment or minimal urethritis (five or more PMNL in a Gram stained endourethral smear[18]) at or after three weeks, treatment was deemed to have failed or the patient to have PGU. If the patient had resumed sexual intercourse with the same partner

before she had completed her treatment or if sexual intercourse had taken place with a new partner, he was assumed to have been reinfected.

Results

Seven patients declined to enter the trial because of the fear of a new drug. We enrolled 66 patients in the study, 10 of whom had to be excluded because five did not return after the initial visit, four attended follow up for less than two weeks from the completion of treatment, and one withdrew from the trial the next day after having second thoughts about the new drug.

STATUS BEFORE TREATMENT

Microbiology

Of the 56 patients evaluated, 22 had gonorrhoea only, seven had combined gonococcal and chlamydial infection, 13 had chlamydial infection only, and 14 had no evidence of either infection. These 14 patients were investigated for *Mycoplasma* spp and *Ureaplasma* spp. *U urealyticum* alone was isolated from six, and a further three patients showed the presence of both *U urealyticum* and *M hominis*.

The MIC of ciprofloxacin for all of the gonococcal isolates was less than 0·01 mg/l, for the strains of *C trachomatis* 1 mg/l to 2 mg/l, for those of *U urealyticum* 0·5 mg/l to 2 mg/l, and for those of *M hominis* 0·25 mg/l to 0·5 mg/l.

Clinical features

Six of the patients were asymptomatic, but all had a demonstrable urethral discharge, which was one of the criteria for enrolment into the trial. The mean duration of symptoms was four days in those with gonorrhoea (with or without chlamydial infection) and 5·8 days in those with NGU. Symptoms and signs were more severe in those with gonorrhoea, but there were no differences between those with chlamydial infection and those with non-gonococcal non-chlamydial urethritis.

Sexual partners:

Of 35 sexual partners who attended our women's clinics, 15 were infected with *N gonorrhoeae* and 15 with *C trachomatis* (including five with combined infection). No STD was detected in seven, but five of these had recently received an antibiotic.

OUTCOME OF TREATMENT

Table I shows the overall results of treatment for each category of infection. Table II shows the results in relation to sexual intercourse during the follow up period as well as to the treatment status of the partner.

Infection with N gonorrhoeae

N gonorrhoeae was cleared in all of the 29 patients whether concurrent chlamydial infection was present or not (table I). Even in the absence of renewed sexual

TABLE I *Results of treatment with ciprofloxacin in 56 patients with urethritis caused by Neisseria gonorrhoeae, Chalmydia trachomatis, both, or neither*

Infective pathogen	No of patients followed up	Persistence or recurrence of:		Persistence or recurrence of urethritis
		N gonorrhoeae	C trachomatis	
N gonorrhoeae only	22	0	1*	9
C trachomatis only	13	0	8	10
Both pathogens	7	0	6	7
Neither pathogen	14	0	0	10

* *C trachomatis* was isolated when this patient was found to have postgonococcal urethritis two weeks after the completion of treatment.

TABLE II *Sexual intercourse during follow up and treatment status of sexual partners in relation to incidence of relapse, isolation of Chlamydia trachomatis again after treatment (numbers in parentheses), or both*

Infective pathogen		No sexual intercourse	Sexual intercourse with same partner: Before partner treated	Sexual intercourse with same partner: After partner treated	Sexual intercourse with new partner	Total
Neisseria gonorrhoeae	Relapse	6	0	1(1)*	2	9(1)*
	No relapse	7	0	2	4	13
Chlamydia trachomatis	Relapse	7(6)	2(1)	1(1)	0	10(8)
	No relapse	1(0)	0	2(0)	0	3(0)
Both pathogens	Relapse	6(5)	1(1)	0	0	7(6)
	No relapse	0	0	0	0	0
Neither pathogen	Relapse	5	0	2	3	10
	No relapse	4	0	0	0	4

* *C trachomatis* was isolated when this patient was found to have post gonococcal urethritis two weeks after the completion of treatment.

intercourse, however, evidence of urethritis persisted or PGU developed in six out of 13 initially chlamydia negative and six out of six initially chlamydia positive patients (table II).

In one patient with gonorrhoea, chlamydiae were isolated at the third follow up visit but had not been isolated before treatment.

Infection with C trachomatis

C trachomatis was isolated after treatment from 14 of the 20 patients with or without concurrent gonococcal infection (table I). Of the 14 patients (six with combined infection and eight with chlamydial infection only) who denied having had sexual intercourse during the follow up period, *C trachomatis* was isolated again from 11 (table II). In none of these were chlamydiae isolated at the first follow up, in five *C trachomatis* was isolated again at the second follow up visit (one week after the completion of treatment), and in a further six at the third follow up visit (two weeks after the completion of treatment). Of the three patients from whom *C trachomatis* was not isolated again, one had to be treated again at the first follow up visit because of persistent overt urethral discharge, another was treated again at the end of three weeks because of persistent urethritis, though his chlamydia swab was negative, and the third remained free of symptoms and signs for up to six weeks, after which he defaulted.

Only four of the 11 patients were symptomatic at the time that *C trachomatis* was isolated again after treatment. In eight the signs of urethritis were minimal — scanty clear discharge demonstrable only on massaging the urethra. Microscopy showed 5 or more PMNL/hpf in all 11 patients. Most had held urine for over four hours. Urethritis persisted or relapsed in 10 of the 13 patients originally infected with *C trachomatis* only.

Non-gonococcal non-chlamydial urethritis

Of the 14 patients evaluated, 10 needed treatment again for persistence or recurrence of urethritis — seven within two weeks after the completion of treatment. Two patients treated again six weeks after the initial treatment were thought to have been reinfected. Though all patients were initially symptomatic, only five had symptoms when they were treated again.

Side effects

None of the patients volunteered that they had experienced any untoward effects. When they were questioned, eight had experienced possible side effects, which were all mild; they included tiredness, sleepiness, insomnia, headache, dizziness, erythema, abdominal discomfort, chest pain, and dry throat. The total serum bilirubin concentration was found to be slightly raised in one patient from 14 μ mol/l before treatment to 22 μ mol/l after treatment (normal 2 to 17 μ mol/l). It had reverted to normal when the test was repeated a week later.

Mycoplasmas

Of the nine patients from whom *U urealyticum* had been isolated before treatment, seven gave a negative result one week after treatment, with only one patient still culture positive. Two weeks after treatment, three patients had become positive for *U urealyticum* and four still remained negative. *M hominis* was not isolated again after ciprofloxacin treatment, and the three patients initially yielding it remained negative throughout the follow up period.

Discussion

It is always difficult to distinguish relapse from reinfection when evaluating the outcome of treatment of an STD. The bias resulting from possibly inaccurate sexual histories can be minimised by cross checking with the case sheets of sexual partners and taking into account the details of sexual history obtained at each visit, as attempted in this study (table II).

Recurrence of chlamydial infections may not be detectable by tissue culture methods until several weeks after treatment, either because of spontaneous periodical variations in the amount of chlamydial growth or because partial antibiotic suppression has reduced the degree and rate of maturation of chlamydiae in persistent foci. This particularly occurs with ß lactam agents.[9] Thus the difficulty in distinguishing relapse from reinfection is even greater than with gonorrhoea, as the patients may well have resumed sexual intercourse in the long follow up period needed.

The optimum follow up period to confirm cure or detect failure for a particular drug regimen in treating chlamydial infection is unknown, but obviously depends on the dose and duration of treatment as well as other factors. In this study, using ciprofloxacin 500 mg twice a day for one week, *C trachomatis* was not isolated again at the first follow-up visit in any of the 14 originally infected patients who denied having had sexual intercourse, and a further two weeks' follow up was necessary to detect all treatment failures.

The minimal signs and absence of symptoms in over half our patients from whom *C trachomatis* was isolated again were consistent with some degree of clinical recovery, possibly due to the partial suppression of *C trachomatis* by ciprofloxacin. The difference between the MIC and the minimum bactericidal concentration (MBC) of ciprofloxacin for *C trachomatis* is known to be at least fourfold.[19] Comparison between the MICs of isolates of *C trachomatis* obtained before and after treatment

showed a twofold increase in four of the five patients investigated. Though a twofold increase is not considered to be appreciable, the one way only trend suggests the possible emergence of resistance during treatment.

There was no opportunity in the present study to compare the efficacy of ciprofloxacin with that of other chemotherapeutic regimens. Nevertheless, the degree of failure of ciprofloxacin to cure chlamydial infection is clearly beyond the normal expectation of routine tetracycline treatment in this and other clinics. Moreover, in a similar study (Arya and Mallinson, unpublished data) of patients seen by the same clinician (OPA) as in the present trial, men with chlamydial urethritis treated with either oxytetracycline 250 mg four times a day for seven days or sustained release tetracycline hydrochloride 500 mg initially followed by 250 mg twice a day for seven days showed, in patients who had not had sexual intercourse, a failure rate of only 14% (two out of 14 treated with oxytetracycline and three out of 22 treated with tetracycline hydrochloride) compared with 78% (11 out of 14 patients) treated with ciprofloxacin in the present study. The difference between the ciprofloxacin regimen and either of the tetracycline regimens was significant ($p < 0.01$). Treatment with oxytetracycline for 14 days resulted in cure in all 15 patients (Arya and Mallinson, unpublished data).

Treatment with ciprofloxacin seemed to be successful in eradicating *M hominis* from the urethras of men, but the same cannot be said for its effect on *U urealyticum*. Seven out of the original nine positive patients were still being followed up two weeks after treatment, and *U urealyticum* was isolated again from three of them. This suggested that, though it seemed to be initially effective, ciprofloxacin was not able to eradicate the organism, which was able to re-establish itself.

We conclude that ciprofloxacin 500 mg twice a day for seven days cures gonorrhoea but is unsatisfactory for aborting postgonoccoccal urethritis and for treating non-specific urethritis, is only partially effective against *U urealyticum*, and is almost completely ineffective against *C trachomatis*. Because of the last observation it was considered unethical to proceed with the clinical trial with the dosage regimen used, and the trial was therefore abandoned.

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